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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/005,469	11/07/2001	Vadim Bichko	0342/1H395US1	7244

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EXAMINER	
LI, BAO Q	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 04/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/005,469	BICHKO, VADIM	
	Examiner	Art Unit	
	Bao Qun Li	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 November 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-22* is/are pending in the application.

4a) Of the above claim(s) *7-8,10-11 and 15-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-6,9 and 12-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/24/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 2-22 are pending.

Response to Amendment

This is a response to the amendment, paper No. 16, filed 11/24/03. Claim 1 has been canceled. Claims 2-6 and 12have been amended. Claims 2-22 are pending. Claims 20-22 have been withdrawn from consideration. Claims 22-6, 9 and 12-14 are considered before the examiner.

Please note any ground of rejection(s) that has not been repeated is removed. Text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Election/Restrictions

In response to the previous Office Action, Applicants amended claims 2-6 and 12,and argue that group II (claim 6-11) and group III (claims 12-19) of inventions should be rejoined with elected group I (claims 1-3 and 5) in the scope of SEQ ID NO: 4. Applicants' argument has been further considered. The restriction/election requirement has been modified as follow:

Claim 2 and claim 12 are linking claims. Claim 2 links claims 6-10 and 11. Claim 12 links claims 13-19. The restriction requirement among the linked inventions is subject to the nonallowance of the linking claim(s), claim 2 or claim 12. Upon the allowance of the linking claim(s), the restriction requirement as to the linked inventions shall be withdrawn and any claim(s) depending from or otherwise including all the limitations of the allowable linking claim(s) will be entitled to examination in the instant application. Applicant(s) are advised that if any such claim(s) depending from or including all the limitations of the allowable linking claim(s) is/are presented in a continuation or divisional application, the claims of the continuation or divisional application may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application. Where a restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. *In re Ziegler*, 44 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

Therefore, during the prosecution, claim 4, 6, 9, 12-14 and 17 with group I. The rest of claims 7-8, 10-11 and 15-22 will not be rejoined until the linking claims 2 and 12 are found in a condition for allowance.

Accordingly, claims 2-6, 9 and 12-14 are considered before the examiner. Claims 7-11 and 15-22 are withdrawn from the consideration.

Claim Rejections - 35 USC § 112

1. Claims 2-3, 5-6 and 12-13 are still rejected under 35 U.S.C. 112, first paragraph on the same ground as stated in the previous Office Action, because the specification, while being enabling for an isolated novel nucleic acid molecule encoding a replication competent recombinant HCV genome I377/NS3-3'UTR having some particular mutations after long time cell culture that is able to replicate efficiently in Huh-7 cell line, does not reasonably provide enablement for having a nucleic acid molecule encoding any full or part of a HCV genome that is able to replicate efficiently when it is transfected into any or all susceptible cell line as listed in claims 3 and 13 without significantly reducing the growth rate of a susceptible cell line by more than 10 folds. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

2. In response to the office action, Applicants cancel claim 1 and amend the claims 2-3 and 5. Applicants submit that now amended claims 2-3 and 5 do not encompass the full universe of heterogeneous HCV-derived nucleic acid, but only those HCV-derived nucleic acids, which encode a replication competent recombinant HCV genome, described in the claims 2-3 and 5.

3. Applicants further argue that the present application provides a detail disclosure of various replication competent nucleic acid molecules derived from HCV I377/NS3-2'UTR and having mutation that lead to their efficient replication in host cells without reducing the host cell growth rate by more than 10 fold. All of these molecules comprise the above-identified structure and functional elements encompassed by the present claims. Applicants further allege that examiner impose an overly high and burdensome duty on applicants. According to the current law and patent practice, the specification can permit some inferences to be drawn by those

skilled in the art, and still comply with the enablement and written description requirement. In other words, there is no requirement that the claims be restricted to the working examples.

4. Applicants also assert since the specification provide the methodology for constructing the HCV replicon and selecting the susceptible cells, it is believed that the present application provides an adequate enablement for the full range of nucleic acids encompassed by claims 2-3 and 5. Accordingly, the 112 first paragraph rejection should be withdrawn.

Applicants' argument has been fully considered; however, it is not found persuasive because the amended claims 2-3 and 5 still read on any or all heterogeneous HCV variants. The specification does not teach how to construct each of these heterogeneous HCV variants. While the method for selecting the susceptible cell line for propagating a transfectant cell harboring HCV replicon is well known in the art, the state of art conclude that it is unpredictable that every cell line is suitable for growing the HCV replicon due to the heterogeneity, transfection of some HCV RNA transcripts are more toxic than to the recipient cells as evidenced by Yoo et al. (J. Virol. 1995, Vol. 69, No. 1, p. 32-38) and Houghton et al. (US Patent No. 5/679,342A). The specification does not give an adequate teaching and guidance for which kind of mutation is able to reduce the toxicity because HCV genome constitutes more than 9000 base pairs, it can be made with enormous mutations along the whole genome. Plus, HCV is an RNA virus, which is susceptible for a very high automotive mutation, which is unpredictable. Therefore, it will result in an undue experimentation for a skilled artisan to predict and practice successful the full scope of the claimed invention. Hence the rejection is maintained.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 2, 3, 4, 5 and 6 are rejected under 35 U.S.C. 102(b) as being anticipated by Lohmann et al. (Science July 1999, Vol. 285-pp. 110-113) on the same ground as stated in the previous Office Action.

7. Applicants traverse the rejection and submit that Lohmann et al. do not anticipate the present invention because, in contrast to examiner's assertion, they do not disclose or suggest to incubate their clones longer under specific selection conditions to achieve the selection of "adapted" HCV clones encompassed by the present claims. Moreover, Applicants asserted that Lohmann et al. teach away from the invention because they concluded that the formation of an "adapted" replicon and cell clones under conditions of their experiments is highly unlikely. The differences between Lohmann et al. and present invention are also clearly shown on page 39 and 40 of current specification. Applicants further argue that in relying upon the theory of inherency, the determination must provide a basis fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art.

8. Applicants' argument has been respectfully considered; however, it is not found persuasive because first, the structural differences between the nucleic acid sequence of Lohmann et al. and that of isolated clones of current application on page 39 and 40 are on cited in all rejected claims.

9. Second, while Lohmann et al. teach that isolation of an adapted clone is hard; however, it is a matter of fact that Lohmann et al. already had the same clones with same sequence structure characteristics to the claimed nucleic acid structure as claims drafted. For instant, the specification discloses that Applicants use same HCV replicon taught by Lohmann et al. to do the transfection. Moreover, according to the sequence analysis, the HCV replicons used by Lohmann et al. exhibit a homology between 99.6% to 99.9% to that of the claimed nucleic acid molecules (See the sequence analysis data), the sequences comprises the 5' and 3' extreme terminal conserved sequences and some kind of modification at the 3' NTR (See 1st col. of page 113). These characteristics all meet the limitations of claims 1-6.

10. Besides the basic facts mention above, technical speaking, a temporary reduction of growth rate is common and normal for any or all cell transfection and single cell cloning experiment. After transfection, it is always take much longer time for the transfected single cell or very light seeded cell to be doubled and reach to growing log phase. It is only when the density of the cloned single cell reach to a certain population and be physically dispersed in the culture dish, the growth rate will eventually catch up approximately to that of the parental cells.

Therefore, it is not comparable between the growth rates between a cloned cell right after transfection with the established culture of that cloned cell. The limitation of growth rate does not constitute a patentable weight because two cloned genes with same genetic characteristics will exhibit same functional properties, and you need to compare them in the same working conditions. Hence the claimed invention is still anticipated by the prior art by Lohmann et al.

11. Claims 2-3, 5 and 12-14 are still rejected under 35 U.S.C. 102(b) as being anticipated by Rice et al. (WO 98/39031A1) on the same ground as stated in the previous Office Action.

12. Applicant traverse the rejection and submit that WO 98/39031A1 does not disclose or suggest to incubate the HCV clones longer under specific selection conditions to achieve the selection of "adapted" HCV clones encompassed by the present claims. Moreover, Applicants allege that according to the review by Marshall accompanying Blight et al. article published on December 2000, they stated that according to Rice, Bartenschlarger's initial system is inefficient, producing HCV protein in only about one in a million host cells. To improve the efficiency, Rice and Blight rebuilt the system using Bartenschlager's data from the GeneBank, looking for genetic mutations that might enable the replicon to be more productive...

13. Applicants further argue that the examiner cannot rely on the concept of inherency based on In re Rijckaert or Ex Parte Levy in that the fact that certain result of characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic.

14. Applicants' argument has been respectfully considered; however, it is not persuasive because the certain structural characteristic of a particular mutation(s) that applicants depend on is not recited in the rejected claims or clearly described in the rejected claims.

15. The limitation of growth rate of host cell harboring the claimed gene does not make any patentable weight because the HCV replicon disclosed by Rice et al. have same characteristics to that of the nucleic acid structure of rejected claims as they are drafted now.

16. Overall, in response to applicant's argument that growth rate of isolated nucleic acid molecule if it is tranfected into a host cell, Applicants are reminded that a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior

art. If the prior art structure is capable of performing the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. See *In re Casey*, 152 USPQ 235 (CCPA 1967) and *In re Otto*, 136 USPQ 458, 459 (CCPA 1963).

17. Moreover, Applicant's arguments do not comply with 37 CFR 1.111(c) because they do not clearly point out the patentable novelty which he or she thinks the claims present in view of the state of the art disclosed by the references cited or the objections made. Further, they do not show how the amendments avoid such references or objections. If Applicants wish to claim an isolated nucleic acid molecule encoding a novel HCV replicon, please amend the claims with precise nucleic acid sequence to overcome the rejection.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bao Qun Li whose telephone number is 703-305-1695. The examiner can normally be reached on 7:00 to 4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 703-308-4027. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Bao Qun Li
Art Unit 1648
April 15, 2004

James C. Housel 4/19/04
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